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A short Review of Recent Advances in Cancer Gene Therapy in relation to Chemotherapy for the Treatment of Breast and Prostate Cancer

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Abstract: Prostate and breast cancer are two of the most common cancers in Western countries. In advanced illness, current treatments are ineffective. Gene therapy has become an essential tool as a result of recent advancements in cancer molecular biology and gene engineering research. Gene therapy is one of the most recent medical breakthroughs, and it offers significant advantages over chemotherapy. Chemotherapy is a treatment that employs powerful chemicals to kill malignant cells in the body that are quickly developing and can harm healthy cells. Cells in numerous regions of your body, including blood, hair, skin, and the lining of your intestine, may be impacted. As a result, adverse effects such as easy bruising and heavy bleeding may occur. Dry mouth and diarrhea mouth ulcers fever fatigue hair thinning a decrease in appetite nausea vomiting discomfort associated with weight reduction, injury, infections, anemia, constipation, and neuropathy are all possible causes. Issues with memory difficulties with concentrating alterations in the skin Insomnia, sexual changes, and fertility problems are all examples of nail alterations. Various gene therapy approaches, pro-drug activating suicide gene therapy, anti-angiogenic gene therapy, oncolytic virotherapy, and gene therapy immunological regulation, and genetic modification of apoptotic and tumor invasion pathways, have been implicated in cancer treatment. The development of more stable and nontoxic gene carriers that encase and transmit foreign genetic elements into malignant cells is known as gene therapy. Some viruses have been tampered with to allow them to transmit genetic material to the host. The transfer of genetic material from one creature to another is carried out via vectors. Adenovirus, herpes simplex virus, and retrovirus are examples of transformed viruses. Researchers are advised to employ cationic in nature, non-viral vectors are frequently cationic in nature. Additionally, there are liposomes and cationic peptides. Conventional liposomes /DNA complexes, such as liposomes/DNA complexes, have not performed as well as the recently introduced preparation of liposomes Liposomes, Protamine, and DNA (lipoplexes). Despite being less effective than viral vectors, non-viral vectors they are safer, simpler to produce, and have a high gene-encapsulating capacity. The purpose of this research is to fill in the gaps in our knowledge about the advantages of cancer gene therapy over chemotherapy in the treatment of breast and prostate cancer.

Keywords: Gene therapy, breast cancer, prostate cancer, vectors, immune modulation

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1. Introduction

Prostate and breast cancer are two of the most common cancers in Western countries. In advanced illness, current treatments are ineffective. Recent advances in cancer molecular biology and gene therapy have made cancer gene therapy a necessary tool.

Gene therapy is one of the most recent medical breakthroughs, and it offers significant advantages over chemotherapy. One of the most important steps in gene therapy is the creation of a gene delivery system that is efficient, safe, and dependable. To transport therapeutic genes to target cells or tissues, a variety of methods might be used. One of the benefits of cancer gene therapy is that it is required. Stable integration, high viral titre, integrates into chromosome 19, less immunogenic, big insert capacity, high transfer, Targets non-dividing cells, large insert capacity, and well-studied molecular activities.

However, when compared to chemotherapy, which is more severe, cancer gene therapy may face problems such as low titre, host immune response, and low efficient transfer.

2. Chemotherapy Overview

Chemotherapy is a treatment that uses strong chemicals to eliminate malignant cells in the body that are rapidly growing and posing a threat to healthy cells. Cells in several parts of your body, such as your blood, hair, skin, and gut lining, may be affected. As a result, complications like rapid bruising and severe bleeding are possible. Infections, anaemia, constipation, neuropathy, lymphedema, memory issues, concentration issues, skin alterations, nail alterations, insomnia, and sexual alterations and fertility changes are all signs of nerve damage. They also include diarrhoea, dry mouth, mouth ulcers, fatigue, fever, hair loss, and loss of appetite. Typically, chemotherapy is administered in conjunction with hormone therapy, radiation therapy, and surgery. This depends on the cancer's stage and type, as well as your general health, previous cancer treatments, cancer cell location, and treatment options.

2.1. Breast carcinoma

In the United States, breast cancer is the most frequent female cancer. In the United States, one out of every nine women is diagnosed with breast cancer. Despite early detection procedures and sophisticated conventional therapies, 46 000 people die each year from breast cancer [1].

The expositions, as well as the molecular sequences and mechanisms involved, clearly demonstrate that breast cancer is a hereditary illness resulting from a succession of cumulative gene damage. Despite the fact that numerous treatment methods for breast cancer have been devised, such as chemotherapy, which has not been demonstrated to be more effective and also has limitations, as a result, new therapeutic techniques for the effective management and treatment of breast cancer are required.

According to [2], several gene therapy plans have been developed for treating breast cancer. Genetic immunopotentiation, proapoptotic gene therapy, molecular chemotherapy, antiangiogenic gene therapy, and mutation compensation and genetic resistance/sensitivity manipulation are the six different treatment modalities. These various gene therapy techniques for breast cancer have been shown to be effective and safe in early-stage clinical trials.

A list of completed, ongoing, and upcoming gene therapy clinical trials for conditions like breast cancer was published by the Journal of Gene Medicine at the beginning of 2003 (http://www.wiley.co.uk/genetherapy/clinical/) [2].

2.2. Genetic elucidation of breast carcinoma

Carcinogenesis may result from a single or multiple chemical, physical, biological, or genetic insults to cells. At least three stages comprise carcinogenesis: initiation, promotion, and progression. Typically, one or more simple mutations, transversions, transitions, and/or minor DNA deletions are responsible for initiating carcinogenesis [3]. Oncogene amplification and chromosomal alterations/loss of tumour suppressor function have been proposed as two key types of genetic modification in breast cancer. The most prevalent form of somatic change seen in human breast cancers is loss of heterozygozity (LOH). [4], [5] LOH refers to a patient's tumour that is heterozygous for the normal cellular DNA marker but loses one allele. When this loss happens at a tumour suppressor gene (TSG) locus and an inactivating mutation in the second allele follows, that is when (as in Alfred Knudson's "two-hit" scenario for retinoblastoma), it is noteworthy. [6][7] LOH has been found on multiple chromosomes in breast cancer, including 1, 3, 4–11, 13, 16–18, 22, and X. [8] [9][10] [11] Losses or deactivation of TSGs could be responsible for the LOH. TSGs are nonfunctional genes that contribute to the progression of cancer. [11] They are primarily negative growth regulators or perform other roles that influence invasiveness and metastasis, Such as adhesion and protease activity regulation. In some cases, the problem is not caused by a TSG mutation, but by another mechanism that inhibits its production or function. One possible cause [2] is methylation of the gene promoter, which inhibits transcription, faster proteasomal degradation, or anomalies in the gene product's interactions with other proteins.

2.3. Gene therapy for breast cancer

Suicide gene therapy is one of the most effective treatments for breast cancer. The two most common types of suicide gene therapy are Toxin gene therapy and enzyme-activating prodrug treatment Toxin gene therapy involves the transfection of genes that generate toxic compounds, whereas enzyme-activating prodrug therapy involves the transfection of genes that generate enzymes that selectively activate specific prodrugs.VDEPT is an acronym for virally directed enzyme prodrug therapy, GDEPT is an acronym for gene-directed enzyme prodrug therapy, GPAT is an acronym for gene prodrug activation therapy, and SGT is an acronym for Gene therapy for committing suicide [12] GDEPT is a two-part treatment for cancer. First, the gene encoding the enzyme is delivered to breast cancer cells. The second stage involves administering a harmless prodrug that is converted into a harmful metabolite by a foreign enzyme expressed in the tumour. In the treatment of breast cancer, two types of enzymes have been proposed for GDEPT. The first group includes nonmammalian 'foreign' enzymes including viral TK, bacterial cytosine deaminase (CD), and carboxypeptidase G2 (CPG2). [12], The second category consists of enzymes derived from humans, such as cytochrome P450 isophorms. [12] thymidine kinase (TK) and CD are two excellent examples of this technique. These enzymes convert ganciclovir (GCV) and 5-fluorocytosine into their pharmacologically hazardous forms.

The toxicity caused by GDEPT should, in theory, be limited to transduced cells. However, due to a phenomenon known as the bystander effect, this may not prove to be as severe as first thought. The bystander effect in GDEPT is the cytotoxic effect of prodrug delivery on non-transduced cancer cells when only a portion of the tumour mass is genetically altered to produce an activating enzyme. [12] Evidence from mouse and human tumour models suggests that they are not identical.

The bystander effect is explained by the transfer of phosphorylated ganciclovir between cancer cells via gap junctions, transduction of endothelial cells within the tumour, and the development of antitumoral immunity [15].

2.4. Gene therapy for prostate cancer

Suicide gene therapy (prodrug activation in transfected cells) and tumour Reversal of the malignant phenotype by introducing normal tumour suppressor genes p53, Rb (retinoblastoma), and p21.HSV-tk in combination with ganciclovir (GCV), 5-fluorocytosine, and cytosine deaminase (5-FC) C-myc and ras expression Oncolytic viral Adenovirus therapy (CN-706, ONYX-015) Retrovirus herpes simplex (G-207) is also considered gene therapy. This section outlines the general concepts of each therapy, with a focus on prostate cancer. The clinical trials of prostate cancer gene therapy that have been submitted to the US Recombinant DNA Advisory Committee are listed in Table 1. (RAC).

Table 1. NIH-Approved Clinical Trials for Prostate Cancer Gene Therapy (as of March 2000)

Category	Strategy	Vector	Transgene	Principal Investiagtor	Principal Investiagtor
Tumor suppressor gene	Direct injection	Adenovirus	p53	C.J. Logothetis	M.D. Anderson Cancer Center, TX
	Direct injection	Adenovirus	p53	A. Belldegrun	UCLA School of Medicine, CA
Suicide gene	Direct injection	Adenovirus	HSV-tk	P.T. Scardino	Baylor College of Medicine, TX
	Direct injection	Adenovirus	HSV-tk	D. Kadmon	Baylor College of Medicine, TX
	Direct injection	Adenovirus	HSV-tk	S.J. Hall	Mount Sinai Medical Center, NY
	Direct injection	Adenovirus	HSV-tk	T.A. Gardner	University of Virginia, VA
Immunomodulation	Vaccine	Retrovirus	IL-2	B. Gansbacher	Memorial Sloan Kettering, NY
(Ex vivo)	Vaccine (Auto)	Retrovirus	GM-CSF	J.W. Simon	Johns Hopkins Oncology Center, MD
	Vaccine	Liposome	IL-2	D. Paulson	Duke University Medical Center, NC
	Vaccine (Allo)	Retrovirus	GM-CSF	J.W. Simon	Johns Hopkins Oncology

					Center, MD
	I.V. dendritic cell	Naked RNA	PSA	J. Vieweg	Duke University Medical Center, NC
Immunomodulation	Intradermal injection	Vaccinia	PSA	A.P. Chen	National Naval Medical Center, MD
(In vivo)	Intradermal injection	Vaccinia	PSA	D.W.Kufe (Phase-1)	Dana-Farber Cancer Institute, MD
	Intradermal injection	Vaccinia	PSA	J.P.Eder (Phase-2)	Dana-Farber Cancer Institute, MD
	Intradermal injection	Vaccinia	MUC1-IL-2	R. Fiblin	UCLA School of Medicine, CA
	Intradermal injection	Vaccinia	PSA	M.G. Sanda	University of Michigan Urology, MI
	Direct injection	Liposome	IL-2	A. Belldegrun (Phase-2)	UCLA School of Medicine, CA
Anti-oncogene	Direct injection	Retrovirus	c-myc	M.S. Steiner	Vanderbilt University Medical, TN
Oncolytic virus therapy	Direct injection	Adeno (CN607)	None	J.W. Simon	Johns Hopkins Oncology Center, MD[16]

2.5. Gene therapy for tumor suppression

P53, RB (retinoblastoma), and p21 are tumour suppressor gene therapies being researched in prostate cancer. [17] [18] Experiments in vitro and in vivo have shown that introducing normal (wild-type) p53 into prostate cancer inhibits malignant phenotype and growth. [19] Despite its theoretical soundness, future practical use is limited by two factors. Because not all prostate tumors have a p53 gene mutation, full tumor regression necessitates transfection of all tumor cells with the p53 gene.

2.6. Suicide gene therapy

Suicide genes produce enzymes that convert harmless prodrugs into lethal metabolites. Viruses, fungi, and bacteria produce the vast majority of these enzymes. An enzyme is produced when a suicide gene is transported into the target cells. Following systemic administration of the specified prodrug, the exogenous enzyme transforms the prodrug into toxic metabolites, resulting in cell death. Once it was believed that the herpes simplex thymidine kinase (HSV-tk) gene was a "tumour suicide gene." When a drug-sensitive gene is transferred, such as HSV-tk, target cells become

susceptible to drug-mediated cytotoxicity (ganciclovir: GCV). Using a gene vector, the viral thymidine kinase gene is delivered to human tumour cells. When GCV is introduced into the system, transfected cells generate intracellular HSV-tk, which is capable of phosphorylating GCV (GCV-P-P-P). The product accumulates within the cell, inhibiting DNA synthesis and causing eventual cell death. The "bystander effect" is one of the potential benefits of combining HSV-tk and GCV in a suicide gene therapy. When a cell dies as a result of gene therapy, the harmful counterpart is transmitted to neighbouring cells via gap junctions or apoptotic vesicles [16].

2.7. Gene therapy modulates the immune system

Tumor vaccine developed in vitro. The most frequently used and well-studied immunomodulatory gene therapy technique is the ex vivo tumor vaccination. Its purpose is to manipulate tumor cells or immune cells to trigger or increase a host antitumor immune response. Antitumor immunity, specifically cell-mediated immunity (the production of tumor-specific cytotoxic T lymphocytes, or CTL), is a multistep process involving numerous cytokines and chemicals. Interleukin-2 (IL-2) and IL-12, as well as granulocyte, macrophage colony-stimulating factor (GM-CSF) are three of the most powerful and well-studied cytokines. [16] The initial tumor, which contains the whole range of tumor antigens, is removed in the gene-modified tumor vaccination technique of cancer therapy. Tumor cells are suspended in a solution, and the a gene vector encoding the cytokine or costimulatory molecules that can induce antitumor immunity is transfected into cells. The patient's transfected cell pool is then expanded, irradiated, and returned. This method has the advantages of not necessitating infection of all tumour cells and systemic response. suggests treatment of the current tumor as well as prevention of recurrence following final treatments such as radical prostatectomy. . However, in the case of prostate cancer, this technique has a substantial drawback in that it needs adequate tumor tissue and effective cell growth.

2.8. Immunomodulatory gene therapy in vivo

A gene vector carrying a cytokine that can eliciting a tumor-specific immune response is injected directly into the tumour or peritumoral region during in vivo immunomodulatory gene therapy. This is an in vivo vaccination against tumours that avoids the drawbacks of gene therapy in vivo (the requirement of sufficient tumour tissue and successful cell culture).

Anti-oncogene therapy is a type of cancer treatment that targets oncogenes. Oncogenes have been discovered as a target for gene modification in prostate cancer. This type of gene therapy employs an antisense oligonucleotide approach. Antisense are synthesized nucleotides that are complementary to a certain RNA sequence and can decrease growth by inhibiting the production of functional gene products (oncogenes).

3. Therapy using oncolytic viruses (virus capable of replication)

When delivered to cancer cells, an oncolytic virus multiplies and destroys the infected cells. Despite the fact that this procedure is not true gene therapy in the sense of targeted gene transfer, it is occasionally referred to as such.

ONYX-015 is a mutated adenovirus that replicates and kills cancer cells. while leaving healthy cells unharmed. [17] The specific mutation of the virus prevents its replication in normal cells. Adenovirus (CN706) has been genetically modified to replicate exclusively in cancer cells that

produce PSA. Enhancer/promoter structures derived from the human prostate-specific enhancer (PSA) gene were utilised to control the replication-required E1A gene, in adenovirus DNA, resulting in the creation of the CN706. CN706 infected human PSA-producing LNCaP cells exhibited significant amounts of E1A, and a single intratumorally injection of CN706 killed An oncolytic virus is a genetically modified or mutant virus that, when delivered to cancer cells, multiplies and kills the infected cells. Although this procedure is not true gene therapy in the sense of targeted gene transfer, it is sometimes referred to as such.

Ex vivo cytokine modification of freshly isolated tumour cells was employed in a number of the earliest cancer gene therapy protocols. Safety concerns and these studies were motivated by unwillingness to directly inject viruses into tumours in situ. It became clear that cytokine modification may not work in the presence of suitable in vivo controls be superior to conventional adjuvant-based cancer cell proliferation treatments without a gene transfer component [20].

4. Conclusion

Cancer gene treatment techniques are a welcome development for current clinical reality and the future, given recent developments and improvements in fundamental medical research. Because of its safety, it will change medical practice, and it will bring unique value to the study of molecular genetics.

References

[1] Lacey Jr JV, Devesa SS, Brinton LA. Recent trends in breast cancer incidence and mortality. Environ Mol Mutagen 2002; 39:82-88.
[2] M A Stoff-Khalili, P Dall & DT Curiel Cancer Gene Therapy . 2006; (13), 633–647.
[3] Pitot HC. The molecular biology of carcinogenesis. 1993; 72(3):962-70.
[4] Osborne RJ, Hamshere MG. A genome-wide map showing common regions of loss of heterozygosity/allelic imbalance in breast cancer. Cancer. Res 2000; 60: 3706-3712.
[5] Miller BJ, Wang D, Krahe R, Wright FA. Pooled analysis of loss of heterozygosity in breast cancer: a genome scan provides comparative evidence for multiple tumor suppressors and identifies novel candidate Regions. Am J Hum Genet 2003; 73: 748-767.
[6] Dickson RBLM. Growth regulation of normal and malignant breast epithelium. In: Bland KI, Copeland III EM (eds). The Breast: Comprehensive Management of Benign and Malign Diseases, 2nd edn. WB Saunders: Philadelphia, 1998; 518–563.
[7] Knudson Jr AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971; 68: 820–823.
[8] Johannsdottir HK, Johannesdottir G, Agnarsson BA, Eerola H, Arason A, Johannsson OT et al. Deletions on chromosome 4 in sporadic and BRCA mutated tumors and association with pathological variables. Anticancer Res 2004; 24: 2681–2687.
[9] Trent JMYJ, Thompson FH, Leibowitz A, Villar H, Dalton WS. Chromosomal alterations in human breast cancer. In: M Sluyser (ed). Growth Factors and Oncogenes in Breast Cancer. Ellis Horwood: Chichester, UK, 1987; 142–151.
[10] Cleton-Jansen AM, Buerger H, Haar N, Philippo K, van de Vijver MJ, Boecker W et al. Different mechanisms of chromosome 16 loss of heterozygosity in well- versus poorly differentiated ductal breast cancer. Genes Chromosomes Cancer 2004; 41: 109–116.
[11] Osborne C, Wilson P, Tripathy D . Oncogenes and tumor suppressor genes in breast cancer: potential diagnostic and therapeutic applications. Oncologist 2004; 9: 361–377.
[12] Niculescu-Duvaz I, Springer CJ . Introduction to the background, principles, and state of the art in suicide gene therapy. Mol Biotechnol 2005; 30: 71–88.
[13] Gadal F, Bastias J, Wei MX, Crepin M . 'Suicide' gene therapy of breast cancer cells is only cytostatic in vitro but anti-tumoral in vivo on breast MCF7-ras tumor. In Vivo 2004; 18: 813–818.

[14] Grignet-Debrus C, Cool V, Baudson N, Velu T, Calberg-Bacq CM . The role of cellular- and prodrug-associated factors in the bystander effect induced by the Varicella zoster and Herpes simplex viral thymidine kinases in suicide gene therapy. Cancer Gene Ther 2000; 7: 1456–1468.

[15] Majumdar AS, Zolotorev A, Samuel S, Tran K, Vertin B, Hall-Meier M et al. Efficacy of herpes simplex virus thymidine kinase in combination with cytokine gene therapy in an experimental metastatic breast cancer model. Cancer Gene Ther 2000; 7: 1086–1099.

[16] Anas El-Aneed. An overview of current delivery systems in cancer gene therapy.Journal of Controlled Release. 2004;(1) 94.

[17] Eastham JA. In vivo gene therapy with p53 or p21 adenovirus for prostate cancer. Cancer Res. 1995; 55: 5151–5155.

[18] Fujiwara T. Therapeutic effect of a retroviral wild-type p53 expression vector in an orthotopic lung cancer model. J Nat Can Inst. 1994; 86:1458–1462.

[19] Gotoh A. Cytotoxic effects of recombinant adenovirus p53 and cell cycle regulator genes (p21 WAF1/CIP1 and p16CDKN4) in human prostate cancers. J Urol. 1997; 158:636–641.

[20] Vile, R., Russell, S. & Lemoine, N. Cancer gene therapy: hard lessons and new courses. Gene Ther .2000; 7, 2–8.